UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION PESTICIDES AND TOXIC SUBSTANCES

TXR NO. 0051423

DATE: December 20, 2002

This report has been revised to correct the Q_1* calculation in accordance with TXR No. 0051402.

MEMORANDUM

SUBJECT: ***MGK® Repellent 326 - Revised*** Report of the Hazard Identification Assessment Review Committee.

FROM: Abdallah Khasawinah
Registration Action Branch 4
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Rebecca Daiss, Risk Assessor
Reregistration Branch 4
Health Effects Division (7509C)

PC Code: 047201

On October 15, 2002, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for MGK® Repellent 326 with regard to the toxicological endpoint selection for use as appropriate in risk assessments. MGK® Repellent 326 is formulated as an insect repellent used in companion animal health care (pets and horses) and personal use. There are no proposed or registered food

uses. The potential for increased susceptibility of infants and children from potential exposure to MGK® Repellent 326 was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document.

Committee Members in Attendance on June 11, 2002

Members present were: Jess Rowland, Elizabeth Doyle, William Burnam, Elizabeth Mendez, Jonathan Chen, Ayaad Assaad, John Liccione, Pamela Hurley, Sue Makris, David Nixon, Brenda Tarplee

Members in absentia were: Steve Knizner

Data evaluation prepared by: Abdallah Khasawinah, Ph.D., RRB4

Also in attendance were: Ray Kent, Susan Hummel, Rebecca Daiss, William Dykstra, Thurston Morton, David Jaquith, Masih Hashim (RD/TRB), Barry O'Keefe (SRRD/RB3), Tawanda Spears (SRRD/RB3), John Bazuin (RD)

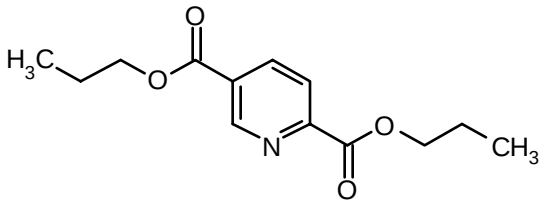
Data Evaluation / Report Presentation: _____

Abdallah Khasawinah

Toxicologist

INTRODUCTION

Chemical Name: MGK® Repellent 326; Dipropyl isocinchromerate



MGK® Repellent 326 is formulated as an insect repellent used in companion animal health care (pets and horses) and personal use to repel biting flies and mosquitoes, gnats, fleas and, ticks. There are no proposed or registered food uses. It has not been considered previously by HIARC or any of its predecessors. On October 15, 2002, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for MGK® Repellent 326 with regard to the toxicological endpoint selection for use as appropriate in risk assessments. The potential for increased susceptibility of infants and children from potential exposure to MGK® Repellent 326 was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document.

I. FQPA - HAZARD CONSIDERATIONS

1. Adequacy of the Data Base for FQPA

The HIARC concluded that the toxicology database for MGK® Repellent 326 is adequate for FQPA considerations. The following studies are available:

-- Developmental toxicity studies in rats & rabbits (acceptable)
-- Two-generation reproduction studies (acceptable)

2. Evidence of Neurotoxicity

The HIARC concluded that there is not a concern for neurotoxicity resulting from exposure to MGK® Repellent 326. There are no neurotoxicity studies available but the chronic and subchronic studies do not indicate neurotoxic effects by this chemical. In a developmental study in rabbits (MRID 40433301), there was a low incidence of clinical signs in some of the dying animals at the highest dose tested: leaning to the left, labored

breathing, involuntary eye movement, dry white material in nasal area, decreased motor activity, and no righting reflex. Several animals that died or were sacrificed *in extremis* displayed no clinical signs of toxicity. These clinical signs of toxicity were considered by HIARC to be **agonal** and not indicative of frank neurotoxicity.

3. <u>Developmental Toxicity Studies</u>

a) <u>Developmental Toxicity - Rat</u>. In an **acceptable/guideline** developmental toxicity (MRID 41987802), MGK® Repellent 326 (Lot # 3716; 98.8% purity) was administered to groups (24/group) of Sprague-Dawley Crl:CD BR mated and presumed pregnant rats (10.5-12 weeks age and weighing 210-286 gm at mating) by oral gavage in 1.0% carboxymethylcellulose suspension at dose levels of 0, 100, 300 or 1000 mg/kg/day from days 6 through 15 of gestation. These doses were selected on the basis of a range finding study (MRID 41987801) where groups of presumed pregnant Sprague-Dawley Crl:CD BR rats were dosed once daily by gavage with MGK® Repellent 326 at dose levels of 0, 100, 200, 400 or 800 mg/kg/day from days 6 through 20 of gestation and no maternal or developmental effects were noted at these dose levels. Therefore the limit dose of 1000 mg/kg/day was selected for the high dose in the main study. The dams were sacrificed on Day 20 of gestation by CO_2 asphyxiation and fetuses removed by cesarean sectioning. No treatment-related mortality, clinical signs or gross pathological observations were noted. The mean gravid uterine weights of the treated groups were slightly lower than the controls suggesting a dose response, but the differences were not statistically significant. The mean gravid uterus weights were 90.6 ± 14, 88.4 ± 19, 86.5 ± 22, 84.5 ± 18 g in the control, low-, mid- and high-dose groups, respectively. A statistically significant decrease in body weight gain (14.5% decrease compared to the control; $p<0.01$) over the 6-15 days of the gestation period was recorded for the 1000 mg/kg/day dose group. Cesarean section observations (abortions, total number of litters, total corpora lutea and corpora lutea/dam, implantations, live fetuses, resorptions, pre- and post-implantation loss and fetal body weight) were comparable to the control group. There were no treatment-related effects on the developing fetuses. No major external/visceral abnormalities were noted in any of the test groups. The **LOAEL** for maternal toxicity of MGK® Repellent 326 in the rat is 1000 mg/kg/day based on reduced body weight gain at this level and the **NOAEL** for maternal toxicity is 300 mg/kg/day. Since no developmental toxicity was observed at the limit dose of 1000 mg/kg/day, the **LOAEL** for this effect is >1000 mg/kg/day and the developmental toxicity **NOAEL** is 1000 mg/kg/day.

b) <u>Developmental Toxicity - Rabbit</u>. In an acceptable/guideline developmental toxicity study (MRID 40433301), MGK® Repellent 326 (Lot/batch # 3716; 100% purity, provided in MRID 42400101) was administered in 0.5% methylcellulose orally via gavage, in a dosing volume of 3 mL/kg, to16 female New Zealand White SPF rabbits/group, at dose levels of 0, 35, 100, or 350 mg/kg/day, on gestation days (GD) 7

through 19. All surviving does were sacrificed on GD 29 and their fetuses were removed by cesarean section and examined. When compared to concurrent controls, no treatment-related changes were observed in the number of corpora lutea, number of implantations, number of live and dead fetuses, number of resorptions, fetal weights, sex ratios, or post-implantation losses at 35 or 100 mg/kg. These parameters could not be evaluated at 350 mg/kg due to high mortality. No treatment-related gross pathological findings were noted at any dose tested. Food consumption was not measured during the study. In the 350 mg/kg/day group, nine does died (GD 9-19) and five does were sacrificed *in extremis* prior to scheduled cesarean section. Clinical signs prior to death included leaning to the left, labored breathing, involuntary eye movement, dry white material in nasal area, decreased motor activity, and no righting reflex. It should be noted that the incidences of these clinical signs were low and were not noted consistently among all animals that died prematurely; several animals that died or were sacrificed *in extremis* displayed no clinical signs of toxicity. These deaths were considered to be treatment-related. Decreased ($p<0.01$) body weight gains were observed during GDs 7-9 (-177 g treated vs. 29 g controls) and GDs 9-12 (-95 g treated vs. 25 g controls). During the second half of gestation and the overall treatment interval, high mortality precluded assessment of body weight gains. In addition, adjusted (for gravid uterine weight) body weights could not be evaluated at this dose.

The maternal LOAEL is 350 mg/kg/day based on mortality preceded by decreased body weight gains. The maternal NOAEL is 100 mg/kg/day. Due to high mortality in the 350 mg/kg/day does, fetal toxicity at this dose could not be evaluated. No fetal toxicity was observed at 35 or 100 mg/kg/day. **The developmental toxicity LOAEL was not observed. The developmental toxicity NOAEL is 100 mg/kg/day.** Based on the dose rationale, no toxic effects were observed in the does at 250 mg/kg/day. Therefore, it would have been preferable if the Sponsor had chosen additional doses between 250 and 350 mg/kg/day for the definitive study in order to demonstrate the sublethal effects of MGK® Repellent 326.

4. <u>Reproductive Toxicity Study Conclusions</u>

<u>Reproductive Toxicity Study - Rat</u>. In an **acceptable/guideline** 2-generation reproduction study (MRID 41547801), MGK® Repellent 326 (Lot/batch #3716; 100% purity) was administered continuously in the diet to COBS® CD® rats (26/sex/dose) at nominal dose levels of 0, 65, 250, or 1000 (limit dose) mg/kg/day throughout premating, gestation and lactation.

Maternal Toxicity. When compared to concurrent controls, no treatment-related changes were observed in the following parameters: mortality, clinical signs, reproductive performance, and gross pathological findings in the F_0 or F_1 adults; mean litter size, viability indices, sex ratios, or gross pathological findings in the F_1 or F_2 pups. Reproductive function was not evaluated in the F_0 or F_1 adults. Anogenital distance, offspring developmental landmarks, organ weights, and histopathology were not evaluated in the F_1 or F_2 pups.

At 1000 mg/kg, decreases in **body weights** occurred throughout premating in the P adults ($p<0.05$ or 0.01) when compared to both control groups. Reductions ($p<0.05$ or 0.01) were also observed in the F_0 females throughout gestation and lactation for the F_{1a} and F_{1b} matings. In the F_1 animals, decreased ($p<0.05$ or 0.01) body weights were observed during the premating interval in the males and females and during gestation and lactation for the F_{2a} and F_{2b} matings. When compared to the mean of both control groups, body weight gains were reduced in the F_0 males and females during the premating interval. During gestation and lactation, body weight gains were decreased relative to the mean of both control groups, but were not statistically different from either control group at any interval. Overall body weight gains were decreased during GDs 0-20 and LDs 0-21 for the F_{1a} and F_{1b} matings; however, the standard deviations associated with the body weight gains were large, and therefore, the decreases were equivocal. In the F_1 generation, decreased body weight gains relative to the mean body weight gains of both control groups were observed in the males throughout the premating interval and in the females during weeks 4-17 only. Overall body weight gains were decreased during GDs 0-20 and LDs 0-21 for the F_{2a} and F_{2b} matings; however, the standard deviations associated with the body weight gains were large, and therefore, the decreases were equivocal.

In the F_0 animals, absolute **food consumption** (g/animal/day) was decreased ($p<0.05$ or 0.01) in the males and females throughout premating. In addition, food consumption was decreased during gestation for the F_{1a} and F_{1b} matings ($p<0.05$ or 0.01). In the F_1 animals, food consumption was decreased ($p<0.05$ or 0.01) in the males and females throughout premating. In addition, food consumption was decreased throughout gestation for the F_{2a} and F_{2b} matings ($p<0.05$ or 0.01), except for days 7-15 for the F_{2a} mating.

During **histopathological evaluation**, trace to mild biliary stasis and portal bile duct proliferation were noted in the livers of the F_0 high dose females. In the F_1 high dose males and females, trace to mild portal bile duct proliferation and trace portal mononuclear cell infiltrate of the liver were observed. In addition, trace to mild bile stasis was observed in the high-dose females. No treatment-related histopathological changes were observed in the F_0 males.

No treatment-related changes were observed in the low- or mid-dose males and females.

The LOAEL for parental toxicity is 1000 mg/kg/day (limit dose) based on decreased body weights, body weight gains, and food consumption and histopathological liver changes in the males and females. The NOAEL is 250 mg/kg/day.

Offspring Toxicity. At 250 mg/kg, **body weights** were decreased in all F_1 pups on PND 21 ($p \leq 0.05$ or 0.01). In addition, body weights were decreased ($p \leq 0.05$ or 0.01) in the mid-dose F_{2b} pups at PND 21.

At 1000 mg/kg, increased numbers of F_1 **pup deaths** relative to controls during PND 0-4 (pre-cull) and PND 4 (post-cull) through 21 were noted. In addition, increased numbers of deaths were noted in the F_2 pups during PND 4 (post-cull) through 21. The most commonly noted clinical sign in the F_1 and F_2 pups was small size. This observation corresponds to decreased body weights noted in these animals. **Body weights** were decreased ($p \leq 0.05$ or 0.01) during PND 1-21 in the F_{1a} and F_{1b} male pups and in the F_{1a} female pups. In the F_{1b} females, body weights were decreased ($p \leq 0.05$ or 0.01) during PND 4 (post-cull) through 21. In the F_2 males and females, body weights were decreased ($p \leq 0.05$ or 0.01) during PND 1-21. Overall (PND1-21) body weight gains (calculated by

reviewers) were decreased in the F_1 and F_2 pups. No treatment-related changes were observed in the low-dose pups.

The LOAEL for offspring toxicity is 250 mg/kg/day based on an decreased pup body weights. The NOAEL is 65 mg/kg/day. The LOAEL for reproductive performance could not be determined because adequate data were not provided.

It is noted that reproductive effects (including decreased testes weights, increased incidences and severity of relative aspermia in the epididymis, aspermatogenesis in the testes, and interstitial cell hyperplasia) occur after prolonged exposure to MGK Repellent 326 as evidenced in the mouse oncogenicity study and the combined chronic toxicity/carcinogenicity rat study.

5. <u>Additional Information from Literature Sources</u>

No information was available in the published literature.

6. <u>Pre-and/or Postnatal Toxicity</u>

The HIARC concluded that there is low concern (and no residual uncertainty) for pre-and/or postnatal toxicity resulting from exposure to MGK® Repellent 326.

A. Determination of Susceptibility.

The HIARC concluded that the available data provided no indication of increased susceptibility (quantitative or qualitative) of rats or rabbits to *in utero* exposure to MGK Repellent 326. However, there is quantitative evidence of increased susceptibility in the 2-generation reproduction study in rats characterized as decreased pup body weight at dose lower (250 mg/kg/day) than that causing parental effects (1000 mg/kg/day). In addition, the effects observed in the offspring at 1000 mg/kg/day (pup death) in this study are more severe than those seen in parental animals (decreased body weight, body weight gain, and food consumption; and liver histopathology changes in males and females) which presents qualitative evidence of increased susceptibility at the highest dose level.

B. Degree of Concern Analysis and Residual Uncertainties.

Since there is evidence of increased susceptibility in the 2-generation reproduction study in rats with MGK Repellent 326, the HIARC performed a degree of concern analysis for the effects seen and evaluated residual uncertainties when considered in context of all available toxicity data. The HIARC determined that there is a low degree of concern (and no residual uncertainty) for the quantitative susceptibility in rat reproduction study because: 1) it is a well conducted study with adequate dosing; 2) there is a well defined pup NOAEL (for the decrease in pup body weight); 3) there is good dose-response for pup effects; and 4) the decrease in pup body weight occurred late during lactation (Days 14-21) when the pups are probably eating significant amounts of feed.

In addition, the HIARC determined that there is a low degree of concern (and no residual uncertainty) for the qualitative susceptibility seen at the highest dose (1000 mg/kg/day) in rat reproduction study because: 1) the more severe pup effects are occurring at the limit dose; 2) in the presence of marked parental effects; and 3) at a much higher dose than that which is selected for regulation and risk assessment (NOAEL = 65 mg/kg/day; LOAEL = 250 mg/kg/day).

C. Special FQPA Safety Factor(s):

Since MGK Repellent 326 is not registered for use in/on foods and has no published or proposed tolerances, the special FQPA safety factor is **not applicable** to risk assessments for this chemical.

7. Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that a developmental neurotoxicity study is not required since there was no evidence of neurotoxicity or neuropathology from the available studies and there is no concern or residual uncertainities for pre/post-natal toxicity.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - MGK® Repellent 326 has no food uses. Therefore, acute reference dose is not applicable.

2. Chronic Reference Dose (cRfD) - MGK® Repellent 326 has no food uses. Therefore, chronic reference dose is not applicable.

3. Incidental Oral Exposure: Short - Term (1 - 30 days)

Study Selected: 2 - Generation Reproduction Study - Rat §83-4

MRID No.: 40433301

Executive Summary: See Section I.4.

Dose and Endpoint for Risk Assessment: 65 mg/kg/day based decreased pup body weight occurring on lactation days 14 - 21 at 250 mg/kg/day.

Comments about Study/Endpoint/Margins of Exposure: This dose and endpoint is protective of the exposed population subgroup (hand-to-mouth behavior in infants and children) and is representative of the exposure duration of concern (effects occurred during Lactation Days 14-21 when pups are probably eating significant amounts of feed).

4. Incidental Oral Exposure: Intermediate - Term (1 - 6 months)

Study Selected: 2 - Generation Reproduction Study - Rat §83-4

MRID No.: 40433301

Executive Summary: See Section I.4.

Dose and Endpoint for Risk Assessment: 65 mg/kg/day based decreased pup body weight occurring on lactation days 14 - 21 at 250 mg/kg/day.

Comments about Study/Endpoint/Margins of Exposure: This dose and endpoint is protective of the exposed population subgroup (hand-to-mouth behavior in infants and children) and is representative of the exposure duration of concern (effects occurred during Lactation Days 14-21 when pups are probably eating significant amounts of feed).

5. Dermal Absorption. There are three dermal absorption studies conducted in human volunteers and one dermal absorption study conducted in rats. These are summarized below.

A. Dermal absorption of formulated MGK® Repellent 326 following multiple applications - human volunteers. In a non-guideline multiple-dose dermal absorption study (MRID 42732101), four healthy male human volunteers (81.3 ± 2.9 kg and age 22 ± 3.6 years) received daily by dermal application 100 uL solution (in isopropanol) of unlabeled MGK® Repellent 326 (1% w/w, lot 3716, purity 99.7%) formulated with both DEET (17.5% w/w, lot# A-1-96, purity 98.8%) and MGK 264 (5% w/w, lot # 3843, purity 100%) at a dose of ~0.012 mg/kg/day (0.042 mg/cm^2) for 14 days. After each application the site was covered for 8 hours after which the protective cover was removed and the site was washed with soap and water and marked for subsequent applications. On the 15th day a similarly formulated dose of pyridine-4-^{14}C- MGK® Repellent 326 (radiolabel code CFQ 5947, radiochemical purity 99%) was applied. One subject was withdrawn from the study on day 14 because of a superficial skin trauma, not related to the study material. After 8 hours of exposure to the radiolabeled material, the protective cover was removed and saved for analysis. The application sites were cleaned with cotton swabs soaked in isopropanol and then rinsed with isopropyl alcohol. The application site was then covered with a gauze pad. At 1, 23, and 45 hours after removal of the test material, tape strippings were performed on the application site and were measured for radioactivity. The subjects were confined to the testing facility for a total of 20 days for test material applications, observations, and sample collections. Urine and feces were collect at intervals throughout the study period for up to 128 hours after application of the radiolabeled dose. No compound-related clinical signs were seen in any volunteer. Mean total recovery of applied dose was 99.28. **Mean dermal absorption of radiolabeled MGK-326 from an 8 hr exposure was 4.75%** (cumulative total measured over 128 hrs). Quantity absorbed is the sum of radioactivity in urine and feces. Absorbed radioactivity was eliminated mainly in the urine and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropyl alcohol swabs (79%). Total unabsorbed dose measured in the swabs, skin rinse and protective cover was 95% of the applied dose. Use of a composite formulation of 17% DEET, 5% MGK-264, and 1% MGK-326 appears reasonable. Based on currently active labels, this formulation is representative of MGK-326- containing repellents sold for personal use. DEET and MGK-326 are the active ingredients in the end use products,

while MGK-264 is used primarily as a synergist. There are no repellent end-use products in which MGK-326 is the sole active ingredient.

B. Dermal absorption of formulated MGK® Repellent 326 following single application-human volunteers. In a non-guideline dermal absorption study (MRID 42974602), four healthy human volunteers (61.1-79.3 kg and age ~ 22 years) were exposed to formulated pyridine-4-^{14}C-MGK® Repellent 326 (non-radiolabeled lot # 3716, purity 99.7%; radiolabeled code: CFQ 5947, radiochemical purity 99%) by a single dermal application of 100 ul of the test solution in isopropyl alcohol at an approximate dose of 0.014 mg/kg (46.6 ug/cm^2) to the test site (4x6 cm section of the volar area of the right or left forearm). The dose formulation contained 1.01% (w/w) MGK-326 (0.7% ^{14}C-MGK® Repellent 326:0.31% non-radiolabeld MGK-326), 17.5% (w/w) DEET (lot# A-1-96, purity 98.8%), and 5% (w/w) MGK® 264 (lot # 3843, purity 100%). The material was left in place under a protective cover for 8 hours. After 8 hours of exposure, the protective cover was removed and the application sites were cleaned with cotton swabs soaked in isopropyl alcohol and rinsed with isopropyl alcohol. The application site was then covered with a gauze pad. At 1, 23, and 45 hours after removal of the test material, tape strippings were performed on the application site and were measured for radioactivity. The subjects were confined to the testing facility for 6 days for observations and sample collections. Urine and feces were collected at intervals throughout the study period for up to 128 hours after application of the dose. Mean total recovery of applied dose was 102.17%. Plasma radioactivity levels indicated that the formulated ^{14}C-MGK® 326 was continuously absorbed through the human skin, and a peak plasma concentration was reached when the exposure was terminated. Plasma radioactivity levels dipped precipitously when the chemical was removed by isopropyl alcohol washing from the skin. **Mean dermal absorption of radiolabeled MGK-326 from an 8 hr exposure was 3.4% (cumulative total measured over 128 hrs).** Quantity absorbed is the sum of radioactivity in urine and feces. Absorbed radioactivity was eliminated mainly in the urine and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropyl alcohol swabs (78%). Total unabsorbed dose measured in the swabs, skin rinse and protective cover was 98% of the applied dose. Use of a composite formulation of 17% DEET, 5% MGK-264, and 1% MGK® Repellent 326 appears reasonable. Based on currently active labels, this formulation is representative of MGK® Repellent 326- containing repellents sold for personal use. DEET and MGK-326 are the active ingredients in the end use products, while MGK-264 is used primarily as a synergist. There are no repellent end-use products in which MGK® Repellent 326 is the sole active ingredient.

C. Dermal absorption of technical MGK® Repellent 326 following single application-human volunteers. In a non-guideline dermal absorption study (MRID 42974601), four healthy human volunteers (74.4-91.7 kg and age ~ 21 years) were exposed to pyridine-4-^{14}C-MGK® Repellent 326 (non-radiolabeled lot # 3716, purity 99.7%; radiolabeld code: CFQ 5947, radiochemical purity 99%) by a single dermal application of 100 ul of the test solution in isopropyl alcohol at an approximate dose of 0.012 mg/kg (41.7 ug/cm^2) to the test site (4x6 cm section of the volar area of the right or left forearm). The application site was covered for 8 hours. After 8 hours of exposure application sites were cleaned with cotton swabs soaked in isopropyl alcohol and rinsed with isopropyl alcohol. The application site was then covered with a gauze pad. At 1, 23, and 45 hours after removal of the test material, tape strippings were performed on the application site and were measured for radioactivity. The subjects were confined to the testing facility for 6 days for observations and sample collections. Urine and feces were collected at intervals throughout the study period for up to 128 hours after application of the dose. Plasma radioactivity levels indicated that ^{14}C-MGK® 326 was steadily absorbed through the human skin, and a peak plasma concentration was reached when the exposure was terminated at 8 hours. Mean total recovery of applied dose was 95.5%. **Mean dermal absorption of radiolabeled MGK-326 from an 8 hr exposure was 24.9% (cumulative total measured over 128 hrs).** Quantity absorbed is the sum of radioactivity in urine and feces. Absorbed radioactivity was eliminated mainly in the urine (24.7% of the applied dose) and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropyl alcohol swabs (48.5%). Total unabsorbed dose measured in the swabs, skin rinse and protective cover was 71% of the applied dose.

D. Dermal absorption of technical MGK® Repellent 326 following single application - Rats. In a dermal absorption study (MRID 42246503), MGK® Repellent 326 (lot # 3716-1, purity 99.5%) mixed with pyridine-4-^{14}C- MGK® Repellent 326 (radiochemical purity 99%) was applied dermally to a group of 5 male, 8 weeks old fasted CD rats to the shaven skin back areas (2.5 x 5 cm). Each rat received a single dermal application of 4 mg/kg (0.08 mg/cm^2) of the test material dissolved in isopropanol. The radioactivity levels in the blood of these rats was determined as a function of time over a 168 hour period by collecting blood from the tail vein. In another experiment, four groups of male rats (5/group) were prepared and treated similarly with a single dermal application of 2.5 mg/kg (0.06 mg/cm^2). These were sacrificed at time intervals corresponding to radiolabeled residues at peak blood levels (1 hr), at half-life (10 hrs), at second half-life (19 hrs), and 168 hours after administration as determined from the first experiment. Blood samples from these groups were collected by heart puncture. Samples of urine, feces, tissues and skin and cage washings were collected for analysis of radioactive dose. Blood levels of radioactivity as a function of time indicated that the test material was absorbed through the skin and rapidly reached a peak level (13% of the administered

dose) at 1 hour after dosing and gradually declining reaching a plateau level after 24 hours. Based on the data from this test, the study author calculated a first half life of 9 hours and a second half life of 19 hours. These values were useful for selecting sacrifice times in the subsequent four treatment group to measure the tissue distribution of radioactive residues as a function of time. Mean recoveries of the test material ranged from (95-103%). The mean percent dermal absorption at selected exposure durations is given in Table 1. Quantity absorbed is the sum of radioactivity in urine, feces, tissues/carcass, and cage wash. **Mean dermal absorption of radiolabeled MGK-326 after 10 hours of exposure was 45%.**

Dermal Absorption Factor: when all the above studies are considered, the most likely dermal absorption factor would be the one derived from human volunteer studies. MGK® Repellent 326 for personal use is always used in formulations with MGK 264 and DEET. Therefore HIARC selected 5% as a dermal absorption factor based on 8-hour exposure measures made in the dermal absorption studies conducted with formulated MGK Repellent 326, in humans.

6. Short-Term Dermal (1 - 30 days) Exposure

Study Selected: 2 - Generation Reproduction Study - Rat §83-4

MRID No.: 40433301

Executive Summary: See Section I.4.

Dose and Endpoint for Risk Assessment: 65 mg/kg/day based decreased pup body weight occurring on lactation days 14 - 21 at 250 mg/kg/day.

Comments about Study/Endpoint: There is no dermal toxicity study conducted with the *formulated* MGK Repellent 326. A 90-day dermal toxicity study with *technical* MGK Repellent 326 conducted in rabbits is available (MRID 42427202), however, due to the problem of skin irritation with the technical, the highest dose tested (HDT) in this study was only 100 mg/kg/day. Since no systemic effects were seen in this study at the HDT and since it is known that effects were produced at this dose in the rabbit developmental study (via gavage), HIARC concluded that, in this case, the route-specific study would not be adequately protective of the offspring effects of concern seen in the 2-generation reproduction study. Therefore the HIARC chose the dose and endpoint from the 2-generation reproduction study in rats (with the 5% dermal absorption factor) to be protective of offspring effects resulting from exposure to MGK Repellent 326 (which are not typically measured in the standard dermal toxicity study).

7. Intermediate-Term Dermal (1 - 6 Months) Exposure.

Study Selected: 2 - Generation Reproduction Study - Rat §83-4

MRID No.: 40433301

Executive Summary: See Section I.4.

Dose and Endpoint for Risk Assessment: 65 mg/kg/day based decreased pup body weight occurring on lactation days 14 - 21 at 250 mg/kg/day.

Comments about Study/Endpoint: There is no dermal toxicity study conducted with the *formulated* MGK Repellent 326. A 90-day dermal toxicity study with *technical* MGK Repellent 326 conducted in rabbits is available (MRID 42427202), however, due to the problem of skin irritation with the technical, the highest dose tested (HDT) in this study was only 100 mg/kg/day. Since no systemic effects were seen in this study at the HDT and since it is known that effects were produced at this dose in the rabbit developmental study (via gavage), HIARC concluded that, in this case, the route-specific study would not be adequately protective of the offspring effects of concern seen in the 2-generation reproduction study. Therefore the HIARC chose the dose and endpoint from the 2-generation reproduction study in rats (with the 5% dermal absorption factor) to be protective of offspring effects resulting from exposure to MGK Repellent 326 (which are not typically measured in the standard dermal toxicity study).

8. Long-Term Dermal (> 6 Months) Exposure. Dose and endpoint was not selected for this exposure scenario since the use pattern (seasonal) does not indicate the potential for long term exposure.

9. Inhalation Exposure: Short and Intermediate Term

Study Selected: 90 - Day Inhalation Toxicity Study - Rat §82-4

MRID No.: 42990201

Executive Summary: In a subchronic inhalation toxicity study (MRID 42990201), groups of 7-week old Sprague Dawley rats (15/sex/dose) weighing 252 gm for the males and 202 gm for the females, were exposed (whole body) to MGK® Repellent 326 (Lot #3716; 100% purity as provided in MRID 42400101, HED # 009831) by inhalation at the analytical concentrations of 0, 0.0105, 0.028, 0.095, or 0.324 mg/L for 6 hours/day, 5 days/week and for a total of at least 67 exposures. The test animals were housed

individually and exposed to the aerosols test material in a 1000 L chamber. Samples were withdrawn from the sampling ports for gravimetric analysis. Samples were also withdrawn from 3 different locations in the chamber to determine the test article distribution within the exposure chamber. Samples were also taken for mass median aerodynamic diameter (MMAD) determinations. The analytical results showed good agreement between targeted, mean gravimetric and analytical concentrations. The means for the average MMAD and the average percentage of particles of ≤ 1.0 µm in diameter were 1.4 µm and 29%, respectively. The test rats were examined twice daily for mortality and clinical signs. Body weights were determined pretest and weekly during the study. Eyes were examined at the pretest period and prior to terminal sacrifice. All animals received postmortem examination. Various hematological and clinical chemistry

parameters were determined for all surviving animals from blood taken at terminal sacrifice time. The lungs of all test animals were examined histologically. Other tissues were examined histologically only from the control and high dose groups.

No compound-related clinical signs of toxicity or mortalities were reported. Two deaths unrelated to the treatment were reported. The test material did not have significant effects on body weights or food consumption. No compound related ocular toxicity or hematological changes were seen in any dosed group. Statistically significant increases in the levels of alkaline phosphatase in males and glucose in females were noted with no apparent dose-related response. No compound related effects were seen in macroscopic examination of the test animals and the various organ weights were comparable to the control group. An increase in the incidence of histological changes were mostly seen in the respiratory tract of test animals. These findings included epithelium-intracytoplasmic eosinophilic material in nasoturbinates and hyperplasia of the mucosa of the nasolarynx, particularly in the high dose animals. These histologic changes were considered adaptive responses to the compound.

Under conditions of this study, MGK® Repellent 326 did not produce any compound-related systemic toxicity. The histopathological changes in the nasoturbinates and the nasolarynx, in the high dose animals were considered to be adaptive responses. The **LOAEL** for MGK® Repellent 326 in this test is **>0.324 mg/L** (60 mg/kg/day calculated based on inhalation rate of 223 L/day and rat weight of 300 g) and the **NOAEL** is **0.324 mg/L (60 mg/kg/day)**. This subchronic 90-day inhalation toxicity study in the rat is classified **acceptable/guideline**, and it satisfies the guideline requirement (OPPTS 870.3465 [§82-4]; OECD 413).

Dose/Endpoint for Risk Assessment: NOAEL of 0.324 L/day (60 mg/kg/day) based on lack of toxicity at this dose.

Comments about Study/Endpoint: Although no toxic effects were seen at the highest dose tested in this route-specific study, the NOAEL (60 mg/kg/day) is comparable to the oral NOAEL of 65 mg/kg/day in the 2-generation reproduction study where effects were seen at 250 mg/kg/day. This dose is protective of the endpoints of concern which include the effects seen in the oral studies and, specifically, of the offspring effects seen in the 2-generation reproduction study in rats.

10. Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	100
Dermal	100	100	100
Inhalation	100	100	100

The target MOE of 100 for **occupational** and **residential** exposure includes only the conventional 100X (10X for interspecies extrapolation and 10X for intraspecies variations).

11. Recommendation for Aggregate Exposure Risk Assessments

Short and intermediate term oral, dermal and inhalation exposure routes can be aggregated since the endpoint of concern (decrease in pup body weight) is the same for oral, dermal (oral equivalent) and inhalation routes of exposure.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

The HED Carcinogenicity Peer Review Committee (CPRC) classified MGK® Repellent 326 as Group B2 - probable human carcinogen with an inadequate evidence in humans (HED memo July 21, 1993). This decision was based on the finding of multiple malignant and benign tumors in the rat and in the mouse. A Q_1^* based on liver adenomas, carcinomas and combined adenomas/carcinomas in rats was derived to be 2.4×10^{-3} $(mg/kg/day)^{-1}$ in human equivalents for the male rat and 1.2×10^{-3} $(mg/kg/day)^{-1}$ in human equivalents for the female rat. The registrant rebutted this classification and requested a second peer review of the carcinogenicity data based on a re-read of the histological slides by a consultant pathologist. However, for the

reconsideration of the previous CPRC cancer classification, the revised pathology diagnosis should be the consensus of a pathology peer review group similar to that employed by the NTP according to Pesticide Regulation (PR) Notice 94-5 dated August 24, 1994. There is no record that such a pathology peer review group had been convened.

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 42093902

Executive Summary: In a combined chronic / carcinogenicity study (MRID 42093902), MGK® Repellent 326 (Lot # 3716; purity 100% provided in MRID 42400101, HED # 009831) was administered to groups (60/sex/dose) of CD® rats (6 weeks old weighing 189-217 g for males and 131-151 g for females) at nominal concentrations of 0 (two control groups A & B used), 65, 250, or 1,000 mg/kg-body weight/day (limit dose) in the diet for 2 years. The doses were selected on the basis of a 13-week range finding study with MGK® Repellent 326 (MRID 42093901) at 0, 125, 250, 500, 1000 or 2000 mg/kg/day where treatment -related effects occurred at 1000 mg/kg/day (decreased body weight gain in males, reduced organ weights) and 2000 mg/kg/day (decreased body weight, mortality, labored breathing, hunched posture, decreased defecation, significant alterations in hematological and biochemical parameters and reduced organ weights) levels.

The test compound did not increase mortality or produce clinical signs or ophthalmoscopic abnormalities, or changes in hematological parameters in any treatment group. A treatment-related statistically significant increase ($p<0.05$-0.01) in the alanine and aspartate aminotransferase levels in the high dose males at various examination periods was noted. The alkaline phosphatase level was also increased ($p<0.05$) in the high dose males at the 24 month examination period. For female rats, the clinical chemistry parameters were similar between the treated and the control groups A & B. A decrease in the pH values was seen in the 1000 mg/kg male and female rats (pH of 6) relative to those of the controls A & B (pH of 7) at various examination periods. Body weights were significantly decreased ($p<0.01$) in high dose males (23% decrease compared to controls A & B) and females (40% decrease compared to both control groups). There was also a 16% reduction in food consumption in males and 24% in females relative to both control groups in the high dose males and females. Food efficiency in high dose males and females was reduced and it was statistically significant ($p<0.05$) at several measurement intervals. A decrease in both absolute and relative (to brain) , liver, heart and kidney weights were seen in both high dose males and females. In addition a significant decrease ($p<0.05$) compared to control groups in absolute and relative (to brain) kidney weights were also seen in the mid-dose group males and females.

Based upon the decreases in body weights, food consumption and food efficiency, and the increased incidence of liver lesions, the highest dose tested (1000 mg/kg/day) had reached the maximum tolerated dose (MTD). In addition, the 1000 mg/kg/day is also considered as the upper limit for an oncogenicity study according to the policy of the HED (Memorandum of Farber to Tox Branch, 7/27/88). The **LOAEL** for chronic toxicity was 250 mg/kg/day based on decreases in the absolute and relative kidney weights in males and females and the **NOAEL** is 65 mg/kg/day.

Discussion of Tumor Data In the high dose group, the test compound produced increases (well above the historical control incidence) in the incidence of hepatocelluar adenomas (16.6% vs 2.5% in combined control males; 13.3% vs 0.8% in combined control females) and carcinomas (16.6% vs 0% control males; 15% vs 0% control females), hyperplastic nodules (6.6% vs 1.7% in combined control males; 11.7% vs 2.5% in combined control females), and foci of hepatocellular alteration of clear cell type (61.7% vs. 17.5% in combined control males; 76.7% vs 11.7% in combined control females). There was also an increase in the incidence of renal cell carcinomas (well above the historical control incidence) in both males (6.7% vs 0%) and females (5% vs 0%) at this dose level. An increase (within the historical control of the laboratory) in the incidence of benign intersitial cell tumors in the testis and in the incidence of benign uterine tumors (polyps) was seen in the 1000 mg/kg males and females, respectively. A re-read of the kidney slides by IRDC (MRID 42973501) did not alter the original findings of renal carcinoma (HED # 011031)

Adequacy of the Dose Levels Tested. Based upon the decreases in body weights, food consumption and food efficiency, and the increased incidence of liver lesions, the highest dose tested (1000 mg/kg/day) had reached the maximum tolerated dose (MTD). In addition, the 1000 mg/kg/day is also considered as the upper limit for an oncogenicity study according to the policy of the HED (Memorandum of Farber to Tox Branch, 7/27/88).

2. Carcinogenicity Study in Mice

MRID No. 42100102

Executive Summary: In a carcinogenicity study (MRID 42100102), MGK® Repellent 326 (100% purity was reported for this lot in MRID 42400101; Lot #: 3716) was administered for up to 80 weeks to 50 CD-1 mice/sex/dose in the diet at nominal dose levels of 0, 0, 125, 500, or 2000 mg/kg/day (2 x limit dose).

No treatment-related effects were noted during clinical observations, ophthalmoscopic examinations, or hematological examination. No adverse effect was observed in the 125 mg/kg/day group. General signs of toxicity were observed at 500 and 2000 mg/kg/day. There was an equivocal effect on the mortality of the 2000 mg/kg/day males where minor to slight increases (incr 9-16%) were observed; however, the effect was not dose-dependent at Week 78. Survival exceeded guideline requirements for an acceptable study. In general, body weights were decreased ($p<0.05$) relative to both concurrent controls in the 500 (decr 3-14%) and 2000 (decr 4-24%) mg/kg/day groups beginning at Week 2 (or Week 40 for the 500 mg/kg/day females), and these decreases persisted until the end of the study. Decreases in cumulative body weight gains were observed in the 500 and 2000 mg/kg/day groups at Weeks 0-2 (decr 33-50 and 100-200%, respectively) and 0-78 (decr 27-43 and 50-63%, respectively). Increased food consumption was observed in the 2000 mg/kg/day group (incr 3-41%; $p<0.05$) generally from Week 5 until study termination. Changes ($p<0.05$) were observed in the reported food efficiencies in all treated groups; however, these changes were sporadic and unrelated to treatment. Nevertheless, body weight gains decreased in the 2000 mg/kg/day group while food consumption increased, which suggested decreased food efficiency.

In the combined animals (n=50), at 500 and 2000 mg/kg/day, the liver was adversely affected in both sexes, and the gall bladder was adversely affected in males. Liver/gallbladder (relative to body) organ weights were increased in both sexes at 500 and 2000 mg/kg/day (incr 7-47% in males and incr 78-113% in females; dose-dependent; $p<0.05$). At 2000 mg/kg/day, liver nodules (gross) were observed in the males (22% treated vs 2-12% controls) and females (32% treated vs 2-4% controls). Liver masses (gross) were observed in the 2000 mg/kg/day males (14% treated vs 4-8% controls). At 2000 mg/kg/day, the following increased incidences were observed: (i) histiocytosis (trace to mild; 62-68% treated vs 0-20% controls) in both sexes; (ii) hypertrophy (trace to moderate; 8-24% treated vs 0% controls) in both sexes; (iii) hyperplastic nodules (10-14% treated vs 0-4% controls) in both sexes; (iv) portal bile duct proliferation (trace to moderate; 22-42% treated vs 0-2% controls) in both sexes; (v) portal mononuclear cell infiltrate (trace to moderate; 38-78% treated vs 2-4% controls) in both sexes; (vi) bile stasis (trace to severe; 58% treated vs 0% controls) in males; (vii) spongiosis hepatitis (trace to moderate; 20% treated vs 0% controls) in males; and (viii) calculus (trace to severe; 52% treated vs 0% controls) in females. Additionally, an increased incidence of histiocytosis in the liver of 500 mg/kg/day males was observed (22% treated vs 0-6% controls). An increased incidence of gallbladder calculus was observed in the 2000 mg/kg/day males (46% treated vs 0% controls).

Slight effects were seen in the reproductive system of the 2000 mg/kg/day males. Decreased testes (absolute and relative to brain; decrease 25-30%; $p<0.01$) weights were

observed. Also, increased incidences and severity of relative aspermia in the epididymis (mild to severe; 32% treated vs 6-14% controls), aspermatogenesis in the testes (trace to severe; 38% treated vs 22-32% controls), and interstitial cell hyperplasia (mild to severe; 10% treated vs 0-2% controls) were observed.

In the combined animals, lung nodules were observed macroscopically in the 2000 mg/kg/day males (32% treated vs 16% controls).

Increased chronic nephritis (trace to severe; 68-72% treated vs 50-54% controls) was observed in the 500 and 2000 mg/kg/day females; however, the severity was not dose-dependent (severe grade: 6-8% treated vs 10-14% controls). Therefore, this was regarded as an equivocal effect.

The LOAEL is 500 mg/kg/day based on decreased body weights and body weight gains in both sexes, increased liver/gall bladder weights in both sexes, and increased liver histiocytosis in males. The NOAEL is 125 mg/kg/day.

Discussion of Tumor Data In the liver of 2000 mg/kg/day females (n=50), an increased incidence ($p \leq 0.001$ compared with both controls; Life Table Test, Incidental Tumor Test, and Fisher's Exact Test) of adenomas (26% treated vs 0% controls) was observed. Positive dose-response trends were detected ($p=0.000$), and the incidence of adenomas exceeded the historical control range of 0-3.33%. Corroborating non-neoplastic pathological evidence of proliferation was observed. In the combined females (n=50) at 2000 mg/kg/day, liver nodules (gross) were observed (32% treated vs 2-4% controls). Microscopically, hyperplastic nodules (10% treated vs 0-2% controls) and portal bile duct proliferation (trace to mild; 42% treated vs 0-2% controls) were observed.

An increased incidence ($p \leq 0.003$ compared with both controls; Life Table Test, Incidental Tumor Test, and Fisher's Exact Test) of alveolar bronchiolar adenomas (48% treated vs 20% controls) was observed in the 2000 mg/kg/day males (n=50). Positive dose-response trends were detected ($p=0.000$), and the incidence of adenomas exceeded the historical control range of 0-31.67%. Following examination of the lung sections, additional lung sections were made. Microscopic examination of these additional sections demonstrated an increased incidence ($p \leq 0.050$ compared with Control A, and $p \leq 0.111$ compared with Control B; Fisher's Exact Test) of alveolar bronchiolar adenomas (48% treated vs 30-34% controls). The incidence of adenomas remained in excess of the historical control range. The incidence of alveolar adenoma in Control B (34%) also exceeded the historical control range; thus, Control A would be most appropriate for Fisher's Exact Test comparison. In the combined animals (n=50), lung nodules were observed macroscopically in the 2000 mg/kg/day males (32% treated vs 16% controls).

Under the conditions of this study, the carcinogenic potential of MGK® Repellent 326 is positive at 2000 mg/kg/day (2x the limit dose). Increased incidences of liver adenomas in females and alveolar bronchiolar adenomas in males were observed.

Adequacy of the Dose Levels Tested Under the conditions of this study, dosing is considered adequate to assess the carcinogenic potential of MGK® Repellent 326 based on decreased body weights and body weight gains in both sexes, increased liver/gall bladder weights in both sexes, and increased liver histiocytosis in males observed at 500 and 2000 mg/kg/day.

3. Classification of Carcinogenic Potential

The HED Carcinogenicity Peer Review Committee (CPRC) classified MGK® Repellent 326 as Group B2 - probable human carcinogen with an inadequate evidence in humans (HED memo July 21, 1993). This decision was based on the finding of multiple malignant and benign tumors in the rat and in the mouse. A Q_1^* based on liver adenomas, carcinomas and combined adenomas/carcinomas in rats was derived to be 1.63×10^{-3} $(mg/kg/day)^{-1}$ in human equivalents for the male rat (TXR No. 0051402).

IV. MUTAGENICITY

MGK® Repellent 326 was tested for bacterial reverse mutation, *in vitro* mammalian cell gene mutation in CHO cells and mouse lymphoma cells and for unscheduled DNA synthesis in rat primary hepatocytes and found negative. These test are summarized below.

MGK® Repellent 326: Mutagenicity Studies

GL #	MRID	Study Type	Results and Classification
84-2 870-5100	40382101	Bacterial reverse mutation September 12, 1986 100% purity 100-5000 µg/plate tested up to cytotoxic dose.	No mutagenic effect was noted with or without microsomal activation at concentrations up to the toxic range of 5000 micrograms of MGK® Repellent 326/plate in the initial tests or in the confirmatory assay. **Acceptable/guideline**
84-2 870-5300	40382102	*In Vitro* mammalian cell gene mutation - CHO cells January 14, 1987. 100% purity 0.0001 - 1.0 µL/ml ± S-9 activated system	MGK® Repellent 326 was negative for the induction of structural chromosome aberrations in the duplicate assays in the presence and absence of metabolic activation (MA) up to toxic dose levels (0.2 uL/mL without MA; 0.5 and 1.0 uL/mL with MA) **Acceptable/guideline**
84-2 870-5300	40382104	*In Vitro* mammalian cell gene mutation - L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay, December 15, 1986 100% purity 0.13-1.2 or 0.024-0.32 µL/mL ± S-9, respectively	MGK® Repellent 326 was tested up to cytotoxic levels (>0.18 µL/mL, -S9 and >0.24 µL/mL, +S9). Increases in mean mutant frequency of at least 2x background with >10% growth were observed in the absence (0.18 µL/mL, trial 4) and presence (1.0 µL/mL, trial 1; 0.9 and 1.2 µL/mL, trial 2) of S9-activation; however, because the results were not reproducible (-S9) and there was no clear dose-response observed in any trial (+ or -S9), the results of the study are considered equivocal **Acceptable/guideline**
84-2 870-5550	40382103	Unscheduled DNA synthesis in Rat Primary Hepatocytes , April 20, 1987, 100% a.i. 0.001 - 0.2 µL/mL tested	MGK® Repellent 326 was tested up to cytotoxic levels (0.06 µL/mL) as determined by increased levels of lactic acid dehydrogenase (LDH) activity. No significant increases in mean net nuclear grains (NNG) or percent cells in repair were observed compared to controls. The positive control, dimethylbenz(a)anthracene (DMBA), induced the appropriate response. **Acceptable/guideline**.

V. HAZARD CHARACTERIZATION

The toxicology data base is adequate to characterize the toxicity of MGK® Repellent 326. MGK® Repellent 326 has low acute toxicity via the oral (Toxicity Category III), inhalation (Toxicity Category IV), and dermal (Toxicity Category III) routes of exposure. MGK® Repellent 326 is not a skin irritant (Toxicity Category IV) or eye irritant (Toxicity Category III). It is not a dermal sensitizer.

Toxic effects by MGK® Repellent 326 in experimental animals occur at relatively high doses. Body weight loss is characteristic of chronic exposures. In mice, doses of 500 mg/kg/day in the diet for 18 months caused decreased body weight and body weight gains in both sexes and increased liver /gall bladder weights in both sexes and increased liver histiocytosis in males. In rats doses of 250 mg/kg/day in the diet for two years caused decreases in the absolute and relative kidney weights in males and females. In dogs dietary doses of 148 mg/kg/day for a year inhibited body weight gain. Higher doses in dogs caused a decrease in the liver and kidney weights, liver histological changes (centrilobular hypertrophy, bile duct proliferation and portal fibrosis). High doses in the diet of rats (1000 mg/kg/day) and mice (2000 mg/kg/day) produced increases in the incidence of liver and renal cell tumors in males and female rats and increased the incidence of liver adenomas in female mice and alveolar bronchiolar adenomas in males. These findings were the basis for classifying MGK® Repellent 326 as a B2 carcinogen - probable human carcinogen by HED CPRC. It should be noted that the carcinogenic effects were seen at the limit dose (rats) or at twice the limit dose (Mice) for carcinogenicity testing. MGK® Repellent 326 was tested for bacterial reverse mutation, *in vitro* mammalian cell gene mutation in CHO cells and mouse lymphoma cells and for unscheduled DNA synthesis in rat primary hepatocytes and found negative. Dietary administration of MGK® Repellent 326 at doses reaching 1555 mg/kg/day for 28 days did not produce peroxisomal proliferation, did not induce peroxisomal enzymes or induce cytochrome P-450 microsomal enzymes (MRID 43033301. Subchronic dietary exposures resulted in decreased body weighs at 1000-2000 mg/kg/day. MGK® Repellent 326 did not cause toxic effects after subchronic exposures through inhalation to 0.324 mg/L (60 mg/kg/day) or through dermal application of 100 mg/kg/day for 90 days. Developmental toxicity occurred at high doses (>1000 mg/kg day in rats; >100 mg/kg/day in rabbits) which were higher than those causing maternal toxicity in rats or rabbits. There were also no indications of teratogenic effects in experimental animals. However there is *quantitative and qualitative* evidence of increased susceptibility of the offspring during *in utero* exposure to MGK® Repellent 326 in a two generation reproduction study in rats. Decreased body weight of pups was noted at 250 mg/kg/day doses compared to the same effect in the parents occurring at 1000 mg/kg/day. Pup mortality was also noted at the 1000 mg/kg/day dose with no parental mortality occurring at this dose.

VI. DATA GAPS / REQUIREMENTS

None

ACUTE TOXICITY

Acute Toxicity of MGK® Repellent 326 (technical)

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral	00155068	LD_{50} = 5850 mg/kg, ♂ 4270 mg/kg ♀ 5120 mg/kg ♂ + ♀	III based on female toxicity
81-2	Acute Dermal	41648601	LD_{50} = > 2000 mg/kg	III
81-3	Acute Inhalation	41571501	LC_{50} = > 6.09 mg/L	IV
81-4	Primary Eye Irritation	41800501	not an eye irritant	III
81-5	Primary Skin Irritation*	41826505	not a skin irritant	IV
81-6	Dermal Sensitization	41648602	not a skin sensitizer	NA

* liquid in aerosol material tested.

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicological Dose and Endpoints for MGK® Repellent 326

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary	Not Established. There are no food-uses at the present time; therefore, an acute dietary risk assessment is not required.		
Chronic Dietary (All populations)	Not Established. There are no food-uses at the present time; therefore, a chronic dietary risk assessment is not required.		
Short-Term Incidental Oral (1-30 days)	NOAEL= 65 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = 100	2-Generation Reproduction-Rat LOAEL = 250 mg/kg/day based on decreased body weight on day 21.
Intermediate-Term Incidental Oral (1- 6 months)	NOAEL= 65 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC = 100	2-Generation Reproduction-Rat LOAEL = 250 mg/kg/day based on decreased body weight on day 21.
Short-Term Dermal (1 to 30 days)	Oral NOAEL= 65 mg/kg/day (dermal absorption rate = 5%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	2-Generation Reproduction-Rat LOAEL = 250 mg/kg/day based on decreased body weight on day 21.
Intermediate-Term Dermal (1 to 6 months)	Oral NOAEL = 65 mg/kg/day (dermal absorption rate = 5%	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	2-Generation Reproduction-Rat LOAEL = 250 mg/kg/day based on decreased body weight on day 21.
Long-Term Dermal (>6 months)	The current use pattern does not indicate potential long-term exposure. Therefore, a dose and endpoint was not selected for risk assessment.		

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Inhalation (1 to 30 days)	Inhalation NOAEL= 60 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	90-Day Inhalation-Rat No toxicity was seen at the highest dose tested (NOAEL). However, this dose is protective of all toxicity seen with this chemical.
Intermediate-Term Inhalation (1 to 6 months)	Inhalation NOAEL= 60 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	90-Day Inhalation-Rat No toxicity was seen at the highest dose tested (NOAEL). However, this dose is protective of all toxicity seen with this chemical.
Long-Term Inhalation (>6 months)	The current use pattern does not indicate potential long-term exposure. Therefore, a dose and endpoint was not selected for risk assessment.		
Cancer (oral, dermal, inhalation)	Classification: B2; Probable human $Q1^* = 1.63 \times 10^{-3}$ $(mg/kg/day)^{-1}$		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.